International Symposium
on Endocrine Disruption 2005

第8回　化学物質の内分泌かく乱作用に関する国際シンポジウム

環境省

プログラム・アブストラクト集
Program & Abstracts

第8回
化学物質の内分泌かく乱作用に関する国際シンポジウム

International Symposium on Endocrine Disruption 2005

2005年12月4日（日）～12月6日（火）
沖縄ハーバービューホテル
沖縄コンベンションセンター

Sunday, December 4 - Tuesday, December 6, 2005
Okinawa Harborview Hotel
Okinawa Convention Center
Okinawa, Japan

主　催：環 境 省
後　援：沖縄県・沖縄県教育委員会・那覇市・宜野湾市・本部町

Organized by: Ministry of the Environment, Government of Japan
Supported by: Okinawa Prefecture, Okinawa Prefectural Board of Education,
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International Symposium on Endocrine Disruption 2005

Program for General Audiences
一般向けプログラム

This program will be in Japanese only.

2005年12月4日（日）

沖縄ハーバービューホテル

Sunday, December 4, 2005

Okinawa Harborview Hotel, Okinawa, Japan

2005年12月4日（日）　［一般向けプログラム］

14:00	**開会挨拶**
14:30-16:00	**パネルディスカッション** **「今、自然界で何が起こっているのか？ ～内分泌かく乱作用から生態系をどう守っていくか～」** コーディネーター：北野　大　（淑徳大学） パネリスト：井口　泰泉（自然科学研究機構） 崎田　裕子（ジャーナリスト・環境カウンセラー） 須之部友基（千葉県立中央博物館） 中山エミリ（タレント） 安間　繁樹（農学博士）

今年、新たにはじめられた環境省の化学物質の内分泌かく乱作用に関する取り組み“ExTEND2005”（「化学物質の内分泌かく乱作用に関する環境省の今後の対応方針について-ExTEND2005-」を短縮して“ExTEND2005（エクステンド2005）”と呼びます）、この重要な柱のひとつが「野生生物の観察」です。

野生生物についてなんらかの異変が観察された場合、異変の原因として内分泌かく乱作用も含めた化学物質の影響が疑われることが少なくありません。しかし、野生生物の異変について判断するためには、まず、そもそもの野生生物の生態を把握している必要があります。また、異変の原因については、温度や日照時間の変化といった自然界の変化、化学物質の影響も含めた様々な人間活動の影響といった、色々な要因を考慮する必要があります。

現在のところ、野生生物について本来の生態が十分に把握されているものは、ごくわずかです。つまり、もし野生生物の異変が報告されたとしても、本当に異常なことなのか、もし異常だとすれば、それがどういった影響（内分泌かく乱作用も候補の一つです）によるものなのか、などが判断しにくいのです。そのため、ExTEND2005では「野生生物の観察」の重要性が強調されています。

そこで、今回のパネルディスカッションでは「野生生物の観察」に焦点を絞り、『今、自然界で何が起こっているか？～内分泌かく乱作用から生態系をどう守っていくか～』をテーマに議論を行います。ディスカッションでは、継続的な野生生物観察を行っている研究者、野生生物の異変と化学物質（特に内分泌かく乱作用）との関連について研究を進めている専門家等、実際の現場に長年携わっている方からの報告VTRをもとに話し合いを進めていきます。

▽報告VTR①「カエルが減っている」　報告者：富岡克寛（地域研究者）
～40年間、群馬県を中心に調査を行っている民間研究者からの、カエルの生息数に関する報告。

▽報告VTR②「状況で変化する野生生物の性別」　報告者：桑村哲也（中京大学教授）
～いわゆる環境ホルモン問題で大きな注目を浴びた、オスがメスに変化するなどの性別の変化。自然界での、この“性別変化”という現象についての研究報告。

▽報告VTR③「英・ローチ研究の今」　報告者：チャールズ・タイラー（英・エクスター大学教授）
井口泰泉（自然科学研究機構 教授）
～イギリスにおける約20年に及ぶ調査研究から分かってきた、ローチ（淡水魚）のメス化の原因についての報告。

出演者一覧

北野　大

淑徳大学 教授

1942年 東京都に生まれる。1972年 東京都立大学大学院工学研究科工業化学専攻博士課程修了(工学博士)。財団法人化学物質評価研究機構企画管理部長を経て1994年 淑徳短期大学食物栄養学科教授、1996年淑徳大学国際コミュニケーション学部経営環境学科教授、2000年　同学科長、2004年 淑徳大学人間環境学科教授に就任。主な著書：『人間・環境・安全』(共立出版)。『循環型社会への提言』(研成社)、他多数。2004年『2004年度日本分析化学会技術功績賞』受賞。

須之部　友基

千葉県立中央博物館

1982年 鹿児島大学水産学部卒業。1984年 鹿児島大学大学院水産学研究科修士課程修了。九州大学大学院農学研究科博士課程修了(農学博士)。1991年 千葉県立中央博物館に勤務。主な著書及び学術論文:『魚類の繁殖行動』(東海大学出版会)、『オキナワベニハゼにおける社会構造と双方向性転換』(Ethology誌)、『オキナワベニハゼの性転 換におけるステロイド合成酵素アロマテースの役割について』(Comparative Biochemistry and Physiology 誌)など多数。

井口　泰泉

自然科学研究機構 教授

岡山大学大学院修士課程修了、東京大学理学博士、1979年 横浜市立大学文理学部助手、1981-83年 カリフォルニア大学バークレー博士研究員、横浜市大助教授を経て1992年 教授に就任。2000年からは基礎生物学研究所教授を経て、岡崎国立共同研究機構・統合バイオサイエンスセンター教授に就任し、現在に至る。マウス、魚やカエルを用いてホルモンや内分泌かく乱物質の発生影響を研究している。日本内分泌撹乱化学物質学会副会長、環境省、厚生労働省、国土交通省などの委員。主な著書：『細胞を中心とした生物学』(広川書店)、『器官形成』(培風館)、『生殖異変』(かもがわ出版)、『環境ホルモンを考える』(岩波書店)、この他アメリカでの著書、学術論文多数。

中山　エミリ

タレント

1978年（昭和53年）生まれ。1995年「ポカリスエット」CFでデビュー。ABC「たけしの万物創世記」TBS「筋肉番付」NTV「速報！歌の大辞テン！！」、TX「ASAYAN」等の司会。舞台では、宮本亜門演出「くるみ割り人形」、パルコ劇場「LOVE LETTER」それぞれ主演。テレビドラマにも数多く出演。現在、CF「三井住友VISAカード」「花王」「タイガー魔法瓶」「丸八真綿」「バイク王」NHK「科学大好き土曜塾」司会、TFM「Amitie du weekend」パーソナリティーに出演中。映画「バッシュメント」2005年12月公開。

崎田　裕子

ジャーナリスト・環境カウンセラー

1974年　立教大学社会学部卒業。(株) 集英社に入社し、11年間雑誌編集を務めフリージャーナリストに。以来、生活者の視点で環境問題、特に「循環型社会づくり」を中心テーマに講演・執筆に取り組むと共に、環境カウンセラー（環境省登録・市民部門）として、環境学習の推進にも広く携わる。また、生活者・NPOの立場で、多数の政策形成の委員会等に参加。環境省、経済産業省、国土交通省、東京都などの委員。NPO法人持続可能な社会をつくる元気ネット理事長、NPO法人新宿環境活動ネット代表理事（新宿区立環境学習情報センター指定管理者)。主な著書：『だれでもできる　ごみダイエット』（合同出版)、『ごみゼロ東京が見えた日』（日報)、『環境ビジネスウィメン』（日経BP）共著、他多数。

安間　繁樹

農学博士

1967年 早稲田大学法学部卒業。法学士。1970年 早稲田大学教育学部理学科(生物専修)卒業。理学士。1979年 東京大学大学院農学系研究家博士課程修了(農学博士)。世界自然保護連合種保存委員会ネコ専門家グループ(IUCN・SSC)委員。熱帯野鼠研究会常任委員、財団法人世界自然保護基金日本委員会(WWF Japan)、財団法人平岡環境科学研究所評議員としても活躍。イリオモテヤマネコの生態研究を最初に手がけ、成果をあげた。1986年以来、国際協力機構(JICA)海外派遣専門家としてボルネオ島の調査および研究指導に携わっている。主な著書：『野生のイリオモテヤマネコ』(汐文社)、『ボルネオ島最奥地を行く』(昌文社)、『琉球列島生物の多様性と列島のおいたち』(東海大学出版会）など多数。

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Program for Experts
専門家向けプログラム

セッション1〜6の全てに同時通訳があります。
Interpretation will be available in Session 1-6.

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Monday, December 5, 2005 (Program for Experts)

9:30-11:45

Session 1 Some Considerations on Epidemiological Studies

P. 12 P. 18

Coordinator: Chiharu Tohyama (Graduate School of Medicine, The University of Tokyo, Japan)

Difficulties in Conducting an Epidemiological Study for Endocrine Disrupting Chemicals
Seiichiro Yamamoto (National Cancer Center, Japan)

Evaluation of Endocrine Disrupters in Women and Children: Lessons from the CHAMACOS and Seveso Women's Health Studies
Brenda Eskenazi (University of California, Berkeley, U.S.A)

Interpreting the Significance of Small Effect Sizes in Epidemiological Studies
David C. Bellinger (Harvard Medical School / Harvard School of Public Health, U.S.A.)

11:45 Lunch

13:00-15:15

Session 2 Risk Communication: Present Status and Future Directions

P. 12 P. 21

Coordinator: Iwao Uchiyama (Graduate School of Engineering, Kyoto University, Japan)

A systematic Guide for Risk Communication with Special Focus on Risk Characterization, Risk Amplification, and Precaution
Peter M. Wiedemann (Research Centre Juelich, Germany)

Risk Communication and Mass Media
Shigeyuki Koide (The Yomiuri Shimbun, Japan)

The Current Status of Risk Communication in Japan
Toshiko Kikkawa (Keio University, Japan)

15:15 Break

15:30-17:45

Session 3 Community and Ecosystem Level Assessment of Human Impacts

P. 13 P. 23

Coordinator: Takayuki Hanazato (Shinshu University, Japan)

Impacts of Endocrine Disruption on Roach, *Rutilus Rutilus*, Populations Living in UK Rivers
Charles R. Tyler (University of Exeter, U.K.)

40 Years of Change on Iriomote Island
Shigeki Yasuma (The Hiraoka Environmental Science Laboratory, Japan)

Biological Interactions: Important Factors in Structuring Organic Communities and Controlling the Pesticide Impact on Ecosystems
Takayuki Hanazato (Shinshu University, Japan)

Tuesday, December 6, 2005 (Program for Experts)

9:30-11:45

Session 4 New Approaches to Mechanistic Understanding of Endocrine Disrupters

P. 13
P. 26

Coordinator: Hajime Watanabe (National Institutes of Natural Sciences, Japan)

Effects of Persistent Organic Pollutants on mRNA Expression in Avian Neuronal and Hepatic Cells Using FRAP-PCR and SAGE
Sean W. Kennedy (National Wildlife Research Centre, Canada)

Germ Cell Apoptosis in Rat Testis is Induced by Oxidative Stress via Oral Administration of di (2-ethylhexyl) phthalate, and is Significantly Prevented by Treatment of Antioxidant Vitamins or Special Six-Carbon Monosaccharides
Masaaki Tokuda (Kagawa University, Japan)

Effects of Estrogenic Chemicals Estimated by Gene Expression Profile
Hajime Watanabe (National Institutes of National Sciences, Japan)

11:45 Lunch

13:00-15:15

Session 5 Development of Testing Methods for Endocrine Disruption

P. 14
P. 29

Coordinator: Taisen Iguchi (National Institutes of Natural Sciences, Japan)

The Validation Management Group for Non-Animal Testing (VMG-NA) of the OECD Task Force for Endocrine Disputing Testing and Assessment (EDTA)
Patric S. Amcoff (Organization for Economic Cooperation and Development (OECD))

Development of OECD Test Guidelines for Endocrine Active Substances in Environmental Species
Anne Gourmelon (Organization for Economic Cooperation and Development (OECD))

Environmental Risk Assessment of Endocrine Disrupters: Status and Needs of Biomarkers
Thomas H. Hutchinson (AstraZeneca R&D, Sweden)

15:15 Break

15:30-17:45

Session 6 Current Initiatives on Risk Assessment of Chemicals

P. 14
P. 32

Coordinator: Hiroaki Shiraishi (National Institute for Environmental Studies, Japan)

Roadmap for Implementing the USEPA Endocrine Disrupter Screening Program
Karen Whitby (U.S. Environmental Protection Agency, U.S.A.)

Developing Approaches to Chemicals Management - A UK View
Michael J. Roberts (Department for Environment, Food and Rural Affairs, U.K.)

Japan's Approach for the Prevention of Environmental Pollution Caused by Chemicals
Satoru Morishita (Ministry of the Environment, Japan)

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講演者一覧

List of Coordinators and Speakers

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List of Coordinators and Speakers

[Session 1]

Chiharu Tohyama (Coordinator)

Professor, Division of Environmental Health Sciences, Center for Disease Biology and Integrative Medicine, Graduate School of Medicine, The University of Tokyo, Japan

Dr. Tohyama obtained Ph.D (toxicology) from the University of Rochester in 1981, and was engaged as a researcher at the NIES since then. He served as the director of the Environmental Health Sciences Division since 1994, and was transferred to the present position in 2005. His research interests range from basic research to health risk assessment, focusing upon dioxins, environmental endocrine disrupters and heavy metals. He also serves at various expert committees of WHO, JECFA, the Ministry of the Environment and Food Safety Commission.

Seiichiro Yamamoto

Head of Biometric Research Section, Statistics and Cancer Control Division, National Cancer Center, Japan

Dr. Yamamoto obtained his B.S., M.S, and Ph.D in Health Sciences from University of Tokyo. He then took a staff position for epidemiology and biostatistics research in National Cancer Center. He was a visiting researcher of the National Cancer Institute in the United States during 2003-2004. His main research field is cancer epidemiology and clinical trial methodology. He is involved in the several large scale epidemiological studies in Japan including the Japan Public Health Center-based prospective Study. He is also a chief biostatistician of JCOG (Japan Clinical Oncology Group), which is a multicenter clinical trial cooperative groups conducting more than 70 trials at present. He is an editorial board member of the Japanese Journal of Clinical Oncology and a board member of the Japanese Society of Medical Oncology.

Brenda Eskenazi

Professor, Maternal and Child Health and Epidemiology, University of California, Berkeley, U.S.A.

Brenda Eskenazi, PhD is a neuropsychologist and epidemiologist whose research interests include the effects of toxicants including lead, solvents, environmental tobacco smoke, dioxin, and pesticides on human reproduction and child development. She directs an NIH/EPA Center for Children's Environmental Health Research (CHAMACOS) and the Seveso Women's Health Study. She is a fellow of the American College of Epidemiology, on the editorial boards of the American Journal of Epidemiology and Environmental Health Perspectives, and on the NAS Board of Children, Youth and Families.

David C. Bellinger

Professor, Neurology / Environmental Health, Harvard Medical School / Harvard School of Public Health, U.S.A

David Bellinger is an epidemiologist and psychologist whose research has focused on the central nervous system effects on children of environmental exposures to metals, including lead, mercury, manganese, and arsenic. He directs a post-doctoral Interdisciplinary Training Program in Neurodevelopmental Toxicology at the Harvard School of Public Health, where he is Professor in the Department of Environmental Health. He is also Professor of Neurology at Harvard Medical School. He has served on numerous committees of the World Health Organization, the U.S. National Academies, and the U.S. Environmental Protection Agency.

[Session 2]

Iwao Uchiyama (Coordinator)

Professor, Department of Urban and Environmental Engineering, Graduate School of Engineering, Kyoto University, Japan

Professor Uchiyama acquired the doctor of medical science after graduating from the University of Tokyo medical department in 1975. He was employed to the National Institute of Public Health in 1982, and was engaged in the research of health effects of air pollution or hazardous chemical substances. Then, he also studies the risk assessment of carcinogenic chemicals, and risk communication about health risk of chemicals. He has taken a present position since 2001. He was given the Japan Society for Atmospheric Environment Award in 2002, and the Japan Society of Risk Analysis Award in 2004.

Peter M. Wiedemann

Director, Program Group MUT, Research Centre Juelich, Germany

Peter Wiedemann, Ph.D., is the Director of the Program Group MUT (Humans, Environment and Technology) at the Federal Research Center Juelich, Germany. He is an internationally recognized expert in the field of risk communication and served as a member of the WHO task force on risk communication (1992-1994), and as the speaker the Scientific Expert Group of the National Action Program "Environment and Health" (1998-2000). Wiedemann was head of the working group "Risk Communication" of the German Association of Engineers (VDI) and contributed to the "OECD Issue Team on Risk Communication" in 2000. He was in 2002-2003 president of the Society for Risk Analysis Europe. He is an elected member of the group "Non-ionizing radiation" of the National Radiation Protection Commission in Germany. Also He is member of the editorial board of "Risk Research" and "Risk, Decision and Policy". Dr. Wiedemann's research focuses on bridging the gap between risk perception research and risk communication on the one side and risk analysis and management on the other side. He is currently performing research in comparative risk assessment, uncertainty analysis, and evidence assessment to provide a basis of sound science for the application of the precautionary principle. His studies are, at the moment, mainly directed to the fields of mobile communications, and biomedicine. Furthermore, Dr. Wiedemann is conducting applied research in issues and crisis management.

Shigeyuki Koide

Senior Editor, The Yomiuri Shimbun; Visiting Lecturer Ochanomizu University

Mr. Koide was born in Tokyo, Japan in 1951. He graduated from the Faculty of Science, Hokkaido University.
After joining the Yomiuri Shimbun in 1976, he served as a reporter in the city news, lifestyle news and science news departments and since June 2005 has become Senior Editor. He reported on the global environment, health care, medicine, atomic energy and basic science issues. In 1995 when the sodium leakage accident occurred on the fast breeder reactor "MONJU", he reported on the process how a false information disclosure could let the trust in science and technology be lost at once. And in 1998 when there was the turmoil on endocrine disrupter causing widespread social jitter and repulse towards chemical substances, he reported on why such misfit occurred between "the truth in science" and "the truth in media reports". He teaches such themes as science and risk-communication issues at the Life World Watch Center at Ochanomizu University.
His leading works are "The Document - MONJU Accident", "Environmental Hormone - What has been known", "Japanese Scientists at the Forefront", "Ten Japanese Nobel Prize Winners" and "Living with Planet Earth - Green Sustainable Chemistry", "Dreams Will Come ? Bill Gates Story".

Toshiko Kikkawa

Associate Professor, Faculty of Business and Commerce, Keio University, Japan

1999 Received Ph.D. from Kyoto University in Psychology
1998 Associate Professor at Keio University, Tokyo, Japan
1995 Assistant Professor at University of Tsukuba, Tsukuba, Japan
1989 Assistant Professor at Kyoto Gakuen University, Kyoto, Japan
1988 Graduated from Kyoto University, Faculty of Letters
Specialized Fields: Risk communication, Simulation games
Crossroad: Kobe -A training tool for risk communication. (in Japanese) (co-authored) Nakanishiya Shuppan (2005)
Risk communication between mineral property developers and local communities. (co-authored) Mining Journal Books, Ltd.: London (2003)
Dealing with risks. (in Japanese) Yuhikaku (2000)
Major publications: Risk communication. (in Japanese) Fukumura Shuppan (1999)

[Session 3]

Takayuki Hanazato (Coordinator/Speaker)

Professor, Director, Research and Education Center for Inland Water Environment, Shinshu University, Japan

Dr. Hanazato graduated from Faculty of Science, Chiba University (Chiba, Japan), in 1980. Researcher in National Institute for Environmental Studies (Tsukuba, Japan), 1980-1995. Professor in Faculty of Science, Shinshu University (Suwa, Japan), 1995-2001. Professor in Research and Education Center for Inland Water Environment, Shinshu University, 2001-present.
Award: The 5th Biwako Prize for Ecology
Books: Cladocera: its ecology and lake environmental problems, Nagoya University Press, 1998.

Charles R. Tyler

Professor, Environmental and Molecular Fish Biology, The Hatherly Laboratories, University of Exeter, U.K.

I have been researching into endocrine disruption and the reproductive physiology of fish for almost 20 years. The research in my team spans studies assessing the impacts of endocrine disrupting (and other) chemicals on fish populations, developing test systems for chemicals in fish, and understanding the mechanistic basis of endocrine disruption, principally using molecular techniques. We have published over 90 full papers in this field of research. I am Director of Research for Biosciences and head Environmental Biology and Ecotoxicology at the University of Exeter. I am the UK supervisor (2005-2010) for the UK-Japan partnership researching into endocrine disruption.

Shigeki Yasuma

Councilor, The Hiraoka Enviromental Science Laboratory, Japan

Education:
1979 University of Tokyo: Doctorate in Agriculture/Wildlife Ecology
1970 Waseda University: Bachelor of Science
1967 Waseda University: B. A. in Law
Work Experience:
1986-2005 Long-term and short-term project expert, JICA
1983-1990 Part-time Lecturer, Kokushikan University.
1983-1985 Chief Researcher, World Wildlife Fund (WWF) Japan Committee.
- Tropical Rain Forest Research Development Project, Indonesia
- Brunei Forestry Project After Care Project, Negara Brunei Darussalam
- Bornean Biodiversity & Ecosystems Conservation Program, Sabah, Malaysia

Awards:
Ichikawa citizen culture UNESCO prize (2004)
Major publications:
Mt. Kinabalu. 152p. Toukai Univ. Press, Tokyo, 2004. (In Japanese)
Borneo Animal Watching Guide. 231pp. Bunichi Sougou Shuppan, Tokyo, 2002. (In Japanese)
Ryukyu Archipelago: Biodiversity.195pp. Toukai Univ. Press, Tokyo, 2001. (In Japanese)
Mammals of Sabah. 181pp. JICA & Sabah Wildlife Department, 1999.
The Natural History of Iriomote Island. 292pp. Shoubunsha, Tokyo, 1990. (In Japanese)
Nansei-shoto and its Conservation. (Co-authored) WWF-Japan, 1984. (In Japanese)
The Wild Iriomote Cat. 228pp. Choobunsha, Tokyo, 1976. (In Japanese)

[Session 4]

Hajime Watanabe (Coodinator/Speaker)

Associate Professor, Center for Integrative Bioscience, National Institutes of Natural Sciences, Japan

B.A. and Ph.D. from the University of Tokyo in 1985 and 1990, respectively. He majored in biophysics, biochemistry and molecular biology. 1991, Research scientist of The Japan Society for the Promotion of Science (JSPS). 1992-1999, Assistant professor, Department of Bioscience and Biotechnology, Tokyo Institute of Technology. 1993-1994, Visiting scientist of Pasteur Institute. 1995-1996 Sub-director, College de France. He is engaged with the present position since 2000.

Sean W. Kennedy

Research Scientist, Environment Canada, National Wildlife Research Centre, Canada

Dr. Sean Kennedy is a graduate (Ph.D., chemistry) of Carleton University. He is a research scientist at the National Wildlife Research Centre of Environment Canada and an adjunct professor in the Department of Biology and the Centre for Advanced Research in Environmental Genomics (CAREG) at the University of Ottawa. His expertise is in the development and application of novel biochemical and molecular biological methods to determine the effects of environmental contaminants on wildlife, with a particular expertise on the effects of contaminants on birds. Dr. Kennedy is also actively involved with international agencies such as the OECD and WHO in efforts to develop internationally-coordinated programs in eco-toxicogenomics.

Masaaki Tokuda

Professor, Faculty of Medicine, Department of Cell Physiology, Kagawa University, Japan

2002 - present	Vice-president, Kagawa University Rare Sugar Research Centre, Kagawa University
1999 - present	Professor, Department of Cell Physiology, Faculty of Medicine, Kagawa University
1995 - 1999	Associate Professor, Department of Physiology, Faculty of Medicine, Kagawa Medical University
1987 - 1995	Assistant Professor, Department of Physiology, Faculty of Medicine, Kagawa Medical University
1984 - 1987	Postdoctoral fellow, Department of Medical Biochemistry, Faculty of Medicine, University of Calgary (Canada)
1983 - 1984	Assistant Professor, Department of Physiology, Faculty of Medicine, Kagawa Medical University
1979 - 1983	Graduate School, Okayama University, Faculty of Medicine
1972 - 1978	Undergraduate School, Okayama University, Faculty of Medicine

[Session 5]

Taisen Iguchi (Coordinator)

Professor, Okazaki Institute for Integrative Bioscience, National Institutes for Basic Biology (NIBB), National Institutes of Natural Sciences (NINS), Japan

MSc at Okayama University and Ph.D. at University of Tokyo. Joined Yokohama City University as an assistant professor in 1979 and promoted to a professor in 1992, Postdoctoral (1981-1983) and a visiting professor at University at Berkeley. In 2000, Professor at NIBB and NINS. Studying developmental effects of estrogen and estrogenic chemicals using various animal species, and persistent changes in mouse reproductive tracts induced by perinatal estrogen exposure. Identifying estrogen responsive genes in mice. Establishing microarray systems of Daphnia magna and American alligator. Cloning steroid receptors from various animal species.

Patric S. Amcoff

Administrator, Test Guidelines Programme, EHS/ENV, Organisation for Economic Cooperation and Development (OECD)

MSc in Ecotoxicology, Uppsala University, Sweden; PhD in Toxicology/Pathology, Swedish University of Agricultural Sciences (SLU); Post-doc, Canada National Water Research Institute, Burlington, Canada; Researcher at SLU in Reproductive Toxicology. Currently work at the Test Guidelines Programme at OECD with Human Health related issues (400-series), animal welfare topics and on screens and in vitro tests for Endocrine Disruption testing.

Anne Gourmelon

Administrator, Environment, Health and Safety Division, Organisation for Economic Cooperation and Development (OECD)

Anne Gourmelon graduated from the Institut Superieur Agricole de Beauvais (France) and obtained a Master in Environmental Sciences from the Wageningen Agricultural University (Netherlands). She has been working at the UN Food and Agriculture Organisation for a few years, before joining the Organisation for Economic Cooperation and Development (OECD) in 2002. She works in the Test Guidelines Programme, in the ecotoxicity area, and also on the development and validation of test methods for endocrine active substances in environmental species.

Thomas H. Hutchinson

Principal Scientist, AstraZeneca R&D, Sweden

Dr. Hutchinson is a biologist with 19 years laboratory and field experience in the environmental risk assessment of pharmaceuticals, chemical products and process effluents. He has a BSc in Environmental Sciences from King's College London, a PhD in Marine Biology from the University of Plymouth and is an elected Fellow of the Institute of Biology (UK). Tom has extensive experience in environmental risk assessment, including ecotoxicology, endocrine disruption and immunotoxicology; he has also published extensively on these subjects. Tom is an active member within several international groups (ECETOC, ECVAM and PhRMA) and he is Co-Chairman of the OECD Validation Management Group for Ecotoxicology (Endocrine Disrupter) test methods.

[Session 6]

Hiroaki Shiraishi (Coordinator)

Director, Research Center for Environmental Risk, Natural Institute for Environmental Studies, Japan

MSc in Chemistry, University of Tokyo; joined National Institute for Environmental Studies (NIES) from 1978 to present, has been studies on environmental chemistry, including chemical analysis, bioassay, exposure assessment, risk of chemicals in the environment. PhD from University of Tokyo in 1985 on environmental analytical chemistry, Postdoctoral (1987) at Indiana University. While studying on fate and transportations of chemicals in the environment from field/laboratory observation and modeling research, recently, worked closely with regulation authority to establish science based risk assessment methodology for chemicals at Research Center for Environmental Risk in NIES.

Karen Whitby

Chief, Registration Action Branch 1 Health Effects Division / Office of Pesticide Programs, U.S. Environmental Protection Agency (EPA), U.S.A.

Dr. Karen Whitby is a Branch Chief in the Health Effects Division (HED) of the Office of Pesticide Programs (OPP) in the US Environmental Protection Agency. Dr. Whitby manages a branch that performs human health risk assessments for dietary and non-dietary pesticide exposures. Dr. Whitby has been with the pesticide program for over fifteen years. For thirteen of those years she has managed staff in the performance of human health risk assessments for new chemicals, new uses of existing chemicals, and reregistration (a regulatory program that evaluates existing chemicals in light of current safety standards). Dr. Whitby has also worked closely with risk managers and performed assessments for chemicals that pose high risks of concern to identify options for reducing exposure and risk.

Michael J. Roberts

Senior Scientific Officer, Chemicals and GM Policy Division, Department for Environment, Food and Rural Affairs (Defra), U.K.

An ecologist by background, I managed the former Department of Environment's marine research programme for several years, providing sientific and technical input to the development of UK marine policy. Currently working for the Chemicals and GM Policy Division of the Department for Environment, Food and Rural Affairs (Defra), I am responsible for provision of advice on endocrine disruption and metals, within the framework of wider UK chemicals policy development. An important part of this work is the supervision of appropriate programmes of research, especially initiatives such as the current UK-Japan collaboration on research into endocrine disruption in aquatic environments.

Satoru Morishita

Director, Chemicals Evaluation Office, Ministry of the Environment, Japan

2005 Director, Chemicals Evaluation Office, Ministry of Environment
2004 Head, Tasl Force for the 3R Initiative, MoE
2003 Deputy Director, Policy and Coordination Division (Global Environment), MoE
2001 Deputy Director, Environmental Health and Safety Division, MoE
1997 Administrator, Environmental Health and Safety Division, Organization for Economic Co-operation and Development (OECD)
1996 Assistant Director, Environmental Activities Promotion Office, Environment Agency (EA)
1992 Assistant Director, Office of Marine Pollution Control and Waste Management, EA
1986 Joined Environment Agency (now MoE)

Kimihiro Iwamoto

Senior Advisor, Environment and Safety Division, Mitsui Chemicals Inc., Japan

1966 Graduated the master course of The Graduated School of Tokyo University.1966 Joined Mitsui Petrochemical Industries Ltd. And Engaged in manufacturing technique management, environment and safety management and quality control.1993 General manager of Environment, Safety and Quality Management Division of Mitsui Petrochemical Industries.1997 General manager of Quality management Division,1998 General manager of Environment and Safety management Division and 1999 Senior advisor on environment and safety. Engaged in the various industry activities such as the member of the environment and safety committee of JCIA, the chairman of the endocrine issue working group of JCIA, the chairman of BPA safety committee of Japanese Manufacturers.

第8回 化学物質の内分泌かく乱作用に関する国際シンポジウム

International Symposium on Endocrine Disruption 2005

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Abstracts

Program for Experts

専門家向けプログラム

2005年12月5日（月）～12月6日（火）

沖縄コンベンションセンター

Monday, December 5 - Tuesday, December 6, 2005
Okinawa Convention Center, Okinawa, Japan

Session 1 Some Considerations on Epidemiological Studies

Difficulties in Conducting an Epidemiological Study for Endocrine Disrupting Chemicals

Seiichiro Yamamoto
National Cancer Center, Japan

There have been a limited number of epidemiological studies conducted to examine the effects of endocrine disrupting chemicals (EDC) on health outcomes. These are even rarer in Japan. In western countries, however, driven by strong interests in the effects of PCB and agricultural pesticide use on humans, several important studies have been conducted, in particular, for breast cancer. These have been cohort studies, using stored serum samples, and large scale case-control studies, with biomarker measurements. These are two possible designs which can provide reliable evidence. These kinds of studies should also be conducted in Asian countries since there exist differences among countries and ethnic groups in: EDC exposure level, incidence of the disease of interest, endogenous hormone level, hormonal drug use, intake of phytoestrogen (such as soy isoflavone), and genetic variability. The purpose of this presentation is to describe the difficulties of conducting epidemiologic studies for EDC, particularly in Japan, from our experiences in conducting a large scale cohort study (more than 140,000 participants) to examine the effects of life style on the disease (JPHC Study), a nation-wide population based case-control study to examine the effects of lifestyle on childhood leukemia and brain tumors, and other studies.

Because randomized controlled trials to examine the effects of EDC on humans are unethical, the most reliable evidence for humans comes from prospective cohort studies involving stored biological samples, such as serum or urine. In these studies, the biggest difficulty is how to ascertain individual health outcomes. Without a legally supported disease registry, it is almost impossible to ascertain individual health outcomes for thousands of people, during long terms of follow up. In Japan, we have no legally supported disease registry for cancer. Our study showed self-reports of cancer and other diseases are not reliable.

An alternative to the prospective study, which is not quite as reliable, is the case-control study, where cases and controls are compared in terms of EDC measurement levels, with adjustment for other, possibly confounding, factors. The biggest difficulty in case-control studies is how to sample representative controls. Ideal controls should be selected randomly from the same population from which cases arise. Unfortunately, however, our experience is that the participation rate by mail requests is about 30%, and this is the common experience in Japan. No analysis can protect against selection bias with this low rate of participation. As a substitute, hospital controls are often selected from the same hospital as cases, but this leads to an underestimate of the risk if the reason for the hospital visit of controls may be associated with the exposure of interest. Our experience indicates that using controls from a different population from cases is often misleading, since exposure distribution in controls varies largely between populations. As for exposure, it is well known that the validity of the estimates is unclear since they are made after the case's diagnosis and may be affected by disease status.

Any of these study designs can provide different results between studies, due to confounding or chance, even if the studies are conducted very well. It is therefore important to validate the results by multiple epidemiologic and biological studies. That is the only way to get reliable evidence.

Despite the difficulties of epidemiological studies for EDC, several studies are being conducted now in Japan. In addition, it is important to establish monitoring systems of exposure and diseases, and also to establish multipurpose cohort studies.

Evaluation of Endocrine Disrupters in Women and Children: Lessons from the CHAMACOS and Seveso Women's Health Studies

Brenda Eskenazi

University of California, Berkeley, U.S.A

There is a growing concern about whether endocrine disrupting chemicals pose a risk for the reproductive health of men and women, and for the health and development of children. Although endocrine disupting chemicals, including PCBs, certain pesticides, and dioxins, have been well-studied in animals, the effects of these chemicals have been poorly studied in human populations. Study of the impact of environmental chemicals on human health is complex. The purpose of this presentation is to present the methodology used to study two populations exposed to endocrine disrupting chemicals, and the key results. We use, as examples, a study, which focused on the reproductive health of women residing in Seveso, Italy and exposed to 2,3,7,8-Tetrachlorodibenzo-*para*-dioxin (TCDD), and another study, which focused on neurodevelopmental functioning in Mexican-American farmworker children living in California and exposed to pesticides which are potentially endocrine disrupting.

In 1976, a chemical plant explosion in Seveso, Italy exposing the nearby residents to the highest exposure to TCDD known in humans. Twenty years later (1996-1998), we initiated the Seveso Women's Health Study (SWHS), a retrospective cohort study, to determine whether exposure increased risk for reproductive disease. We enrolled almost 1000 women who lived near the chemical plant and who had blood stored since 1976. As part of this study, we measured TCDD in the stored specimens, and women received an interview, gynecologic exam with pelvic ultrasound, completed a menstrual diary, and had a blood draw. The median serum TCDD was 55.8 ppt, (range: 2.5 - 56,000), with higher levels in those that were young. We have examined the relationship of TCDD in blood and spontaneous abortion, infantbirth weight, menstrual cycle characteristics, age at menarche and at menopause, endometriosis, fibroids, and breast cancer. We will present a summary of the findings of the SWHS to date.

The second example will be from the CHAMACOS project, a longitudinal birth cohort study that enrolled 600 primarily low-income Mexican immigrant farmworker pregnant women living in the agricultural Salinas Valley, California. Over 500 children were born and most have been followed until 5 years of age. Mothers were interviewed twice during pregnancy, at delivery, and when the children were 6 months, 1, 2, and 3.5 years of age. Urine, blood and breastmilk samples were collected. Neurodevelopmental assessments of the children and home inspections were conducted at each age. Currently, we are conducting visits with the children at 5 years of age. The aims of the Center include 1) assessment of pesticide exposure in pregnant women and young children; 2) the potential health effects of pesticides on childhood growth, neurodevelopment and respiratory disease; 3) the mechanisms of pesticide neuro- and immuno-toxicity; and 4) community-based outreach and interventions to reduce take-home pesticide exposure to children of farmworkers. We will present a summary of the findings of the CHAMACOS study to date.

Interpreting the Significance of Small Effect Sizes in Epidemiological Studies

David C. Bellinger

Harvard Medical School / Harvard School of Public Health, U.S.A.

The sizes of the putative effects observed are often small in studies that rely on functional endpoints such as neurodevelopment as the critical health effects. Because the mean deficits implied are more modest in magnitude than are those that correspond to the clinical criteria used to diagnose "disease," some observers dismiss them as inconsequential. The mean deficits take on greater import when viewed as effects on a population rather than on individual members of the population. Several considerations germane to an effort to reconcile these perspectives will be discussed: (1) the relative sensitivity of clinical diagnoses and continuously distributed scores on neurobehavioral tests as indices of adverse effect, (2) the syndromal nature of many diagnoses in behavioral neurology and the implications of shifting nosology, (3) the role of neurobehavioral test score scores as markers of or as prodromes for clinically significant deficits, (4) the implications of the distinction between individual risk and population risk, and (5) the tendency of the distributions of a risk factor in population to move up and down as a whole. The clinical and population perspectives on neurobehavioral toxicity are complementary rather than incompatible.

Session 2 Risk Communication: Present Status and Future Directions

A Systematic Guide for Risk Communication with Special Focus on Risk Characterization, Risk Amplification, and Precaution

Peter M. Wiedemann
Research Centre Juelich, Germany

The paper deals with four major challenges faced by risk communicators: (1) how to provide a transparent, consistent, and reasonable risk characterization, (2) how to communicate uncertainties, (3) how to deal with risk amplification, and (4) how to justify appropriate precautionary actions?

Risk communication is a fundamental component of the risk analysis paradigm. Not only is risk communication necessary among experts of various disciplines in order to assess the risks, but also is an essential tool for bi-directional sharing of information, values, and preferences between experts, decision-makers, stakeholders and the public. In this light, it is sensible and - indeed - crucial for the risk communication efforts to integrate a sound risk characterisation. I propose an "evidence framework", that allows for a transparent summarization of the experts' line of reasoning. This framework helps to describe the most crucial arguments for as well as against a risk suspicion, the conclusions of the experts, and the remaining uncertainties.

However, social science research on risk demonstrates that basing risk communication solely on a scientific risk characterization falls short of the mark. The current social perception and potential for emotional and social risk amplification, as well as their dynamics, must also be considered.

Furthermore, a successful risk communication program should also focus on the risk management strategies. Special attention deserves the question "How will people react to the implementation of the precautionary measures?". The key is the impact of precautionary measures on risk perceptions.

My proposals for risk communication that address these critical issues will be based on our recent empirical research into risk perception and risk communication.

The Current Status of Risk Communication in Japan

Toshiko Kikkawa
Keio University, Japan

The author reports the current status of risk communication in Japan. Although the concepts of risk and risk communication, and even the concept of communication, were not well recognized in the Japanese society, risk communication has been becoming one of the major concerns these days.

As to the topic of endocrine disrupters, in the early stage of risk communication on the endocrine disrupting chemicals, they are introduced as, to some extent, 'unknown' risks. The communication seemed to fail in the sense it caused a nationwide scare at that time. The scare was mainly attributed to the 'sensational' journalism and was in part attributed to the so-called 'emotional' laypersons. However, the author knows of no empirical data supporting such a contention. More plausible explanation could be that the ambiguous nature of risks of endocrine disrupters would lead people to act in a rather conservative way to refuse technology.

In addition, the author and the colleagues did a national survey to grasp the current attitudes toward endocrine disrupters among the Japanese. The main findings were as follows: (1) While approximately 2/3 of the respondents had never heard of the technical term "endocrine disrupting chemicals", approximately 90% of them knew of the term "environmental hormone" instead, which is not scientifically correct. (2) Whereas the need for information was potentially high, scientifically incorrect knowledge (what is called "laypersons' knowledge") was very common. (3) More than 70% of the respondents did not know the fact that the relation between endocrine disrupters and human health damage has not yet been scientifically proven.

The interpretation of the above-mentioned results could be that the interest in endocrine disrupters among Japanese has decreased recently and the knowledge of endocrine disrupters has not yet reached to the satisfactory level.

As is usual the case with other risks containing ambiguity, the conflict between risk experts and laypersons exists in the endocrine disrupters. There could be a sharp difference between risk experts and laypersons over the preference in precautional measures in particular and/or the evaluation of risk assessment in general.

In conclusion, a new way of risk communication is necessary to establish mutual understanding and to encourage all the stakeholders including laypersons to actively involve in risk communication of the endocrine disrupters.

Session 3 Community and Ecosystem Level Assessment of Human Impacts

Impacts of Endocrine Disruption on Roach, *Rutilus Rutilus*, Populations Living in UK Rivers

Charles R. Tyler
University of Exeter, U.K.

Endocrine disruption is now a well-established phenomenon in both freshwater and marine fish. One of the most common effects reported in fish is the feminisation of males and some of the most comprehensive studies in this regard have been conducted on wild roach, *Rutilus rutilus*, living in UK Rivers. Over the past 10 years we have established that intersex (the simultaneous presence of males and female features in the same gonad) occurs commonly in wild roach in rivers contaminated with wastewater treatment works (WwTWs) effluents and this condition can be induced experimentally on exposure to oestrogenic effluents and to some individual oestrogenic chemicals. We have also shown that some of the oestrogenic chemicals of concern bioconcentrate in roach. Importantly, roach with altered gonadal development have an altered timing to maturation and/or produce gametes of poorer quality with a reduced capacity for fertilisation. Thus the ability of feminised male roach to reproduce is compromised and, depending on the severity of the condition, individuals can be rendered infertile. Given that feminisation of male roach in UK Rivers is extensive - a recent survey identified intersex roach at 44 out of 51 sites studied throughout England and at some of these sites all males were feminised, a population level impact is a very real possibility. Roach comprise up to 50% of the lowland UK freshwater fishery, thus endocrine disruption could also fundamentally affect the riverine freshwater ecosystem.

In the second part of my presentation I will focus on the challenges we now face in trying to understand the population level consequences of endocrine disruption in wild roach. In the first instance we need to develop a more complete understanding of the basic breeding biology of the roach, of which we know very little, because the parentage dynamics could have a major bearing on how the population is impacted by endocrine disruption. For example, if in natural populations only a small percentage of the males contribute their gametes to the gene pool, then a certain level of intersex can likely be accommodated without harm to the population. If on the other hand gametes from most reproductively active males contribute, then endocrine disruption might serve to reduce the normal genetic heterogeneity of the population. For other fish species, we have evidence to show that reproductively compromised males compete in the spawning act with other males and can alter the breeding capabilities of other 'fit' males. The importance of age in breeding roach populations is also not known and given the fact the severity of the intersex condition in fish in effluent contaminated rivers increases with age, this could also have a major bearing on the reproductive success of the population. We are developing DNA microsatellite markers in roach and propose to experimentally manipulate breeding colonies to address some of these questions. Other questions we need to address in developing our understanding of the population level effects of exposure to endocrine disrupting chemicals (EDCs) include how fish might acclimate and adapt to EDCs in the aquatic environment. Until we have this information our ability to predict roach population and thus ecosystem level impacts of EDCs, even with modelling approaches, is limited.

40 Years of Change on Iriomote Island

Shigeki Yasuma

The Hiraoka Environmental Science Laboratory, Japan

An island is conceptually easy to grasp as an ecosystem. It is an isolated, stable ecosystem without external influences, but is also fragile if external influences penetrate.

Evidence suggests that there was human settlement on Iriomote Island from at least around the 8th century and human activity has been continuous since then. Although there has been a long history of the construction of new villages by immigrants and the demise of other villages due to malaria, it is true to say that the coexistence between the environment and humans has been maintained with little adverse environmental impact.

Ten years after the end of the Second World War and after malaria was eradicated, immigration restarted and Iriomote Island began to change.

I have been observing the natural environment of Iriomote Island since 1965, when the Iriomote cat was first discovered. In those days there was no road linking the east and west coasts of the island. About 3000 people lived on the island but the environment was preserved, a variety of shellfish could be found in the sea and the fishing catch was plentiful. In 1972 Okinawa returned to Japan. After that, the population of Iriomote decreased and the population remained at about 1200 into the 1980s.

About 1800 people live on the island now. The harbor and road have been upgraded and the number of cars has increased, power and water are supplied throughout the island and a fairly comfortable standing of living is guaranteed. On the other hand, exotic plants have increased, including Spanish needles (Bidens), and the native vegetation of Iriomote is disappearing along the road. The presence of exotic animals such as the giant toad (Bufo) etc. has been confirmed. The fishing catch has reduced.

In my estimation, the Iriomote cat population has remained at about 80-100 animals since it was first discovered, but the causes of death have greatly changed. Dog attacks and trapping used to be the main factors, but now most Iriomote cat deaths are caused by traffic. This is one example of the adverse effect of humans on the environment and this effect is increasing. Such impact was inconceivable twenty years ago. These effects are easy to understand because there is clear physical evidence in front of us. However, the effects on the ecosystem of chemical substances and environmental hormones are difficult to see, so often countermeasures are taken too late. However, we should be aware that they are advancing quietly and deeply even though we can't see them.

There are three important steps to ensuring coexistence between the natural environment and humans, although of course it is not easy for people who know convenience to return to the old ways. The first is to take effective protective measures for protected areas and to develop designated development areas efficiently, the second is to put limits on the amount of road construction and development, and the third is to control the introduction of pets, foliage plants and other exotic organisms.

Biological Interactions: Important Factors in Structuring Organic Communities and Controlling the Pesticide Impact on Ecosystems

Takayuki Hanazato
Shinshu University, Japan

Biological interactions, such as predator-prey and competition, are very important in structuring the lake zooplankton communities. For example, fish induce the development of zooplankton community dominated by small-sized species such as small cladocerans and rotifers by selective predation on large-sized species. On the other hand, large-sized species dominate the zooplankton communities in lakes with less abundant fish, because the large species out compete the small ones by competition for food.

The large zooplankton species tend to be more sensitive to toxic chemicals than small ones. It would be expected, therefore, that the contamination with pesticides in lakes reduce the large species but increase the small species, which are released from competitive pressure by the large species. The increase of the small species is a result of the indirect effect of pesticides through biological interactions. The indirect effect should be understood in assessing the pesticide impact on ecosystems.

To analyze the indirect effect, we performed a mesocosm experiment using experimental tanks, where a zooplankton community was established in the tanks with different densities of the predator cyclopoid copepoda, and was exposed to the insecticide carbaryl. Rotifer populations showed different responses to the carbaryl application between the tanks of different predator densities. They decreased largely in the tanks with abundant predators due to mortality caused by the pesticide toxicity and predation. In contrast, they increased in the tanks with low density of predators, because the rotifers were released from the competitive pressure by cladocerans, which were damaged more intensively by the pesticide than rotifers.

Impacts of biological interactions (natural factors) and of toxic man-made chemicals (anthropogenic factors) on ecosystems are discussed.

Session 4 New Approaches to Mechanistic Understanding of Endocrine Disrupters

Effects of Persistent Organic Pollutants on mRNA Expression in Avian Neuronal and Hepatic Cells Using FRAP-PCR and SAGE

Sean W. Kennedy, Doug Crump and Stephanie P. Jones
National Wildlife Research Centre, Canada

In recent years there has been considerable interest in using new methods for assessing the effects of endocrine-disrupting chemicals (EDCs) on gene expression in wildlife species in much the same way that the methods are being developed and applied for human toxicology. With wildlife species there are many important scientific and technical challenges for adopting such approaches. The DNA sequences for critical genes that are known to be impacted by EDCs are not available for most wildlife species, thus limiting the application of large-scale studies with cDNA microarrays in most laboratories. In our laboratory, we are exploring the possibilities of using 'open' methods of mRNA expression for determining the effects of selected persistent organic pollutants such as polybrominated diphenyl ether (PBDE) flame retardants and perflurorinated organics in wild birds. Our studies involve both examining the effects of EDCs *in* ovo and in primary cultures of neuronal cells (from the cerebral cortex) or hepatic cells. The molecular methods that we are using include a new Fluorescent Arbitrarily Primed PCR (FRAP-PCR) technique and Serial Analysis of Gene Expression (SAGE). In this presentation, we will describe the methods, and will present some of our recent results that have been used to discover novel effects of PBDEs and 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) on mRNA expression in avian neuronal and hepatic cells.

Germ Cell Apoptosis in Rat Testis is Induced by Oxidative Stress via Oral Administration of di (2-ethylhexyl) phthalate, and is Significantly Prevented by Treatment of Antioxidant Vitamins or Special Six-Carbon Monosaccharides

Masaaki Tokuda, Shigeru Suna, Fuminori Yamaguchi and Fumihiko Jitsunari

Kagawa University, Japan

Phthalate esters have been used extensively as plasticizers of synthetic polymers. Recent studies have revealed that these esters induce atrophy of the testis, although its pathogenesis remains unknown. The present study describes the possible involvement of oxidative stress in the pathogenesis of atrophy of the rat testis induced by di (2-ethylhexyl) phthalate (DEHP).

Liver enlargement occurred in rats fed either a 1 or 2 % DEHP-containing diet in two weeks. However, testicular atrophy accompanied by aspermatogenesis was induced by feeding with the 2% but not with the 1% DEHP-containing diet. This suggests that the critical DEHP dose for gonadotoxicity is higher than that for hepatotoxicity.

Biochemical and immunohistochemical analysis revealed that oral administration of DEHP increased the generation of reactive oxygen species, with concomitant decrease in the concentration of glutathione and ascorbic acid in the testis, and selectively induced apoptosis of spermatocytes, thereby causing atrophy of this organ. Oxidative stress was selectively induced in germ cells, but not in Sertoli cells, treated with mono (2-ethylhexyl) phthalate (MEHP), a hydrolysed metabolite of DEHP. Furthermore, MEHP selectively induced the release of cytochrome c from mitochondria of the testis. These results indicate that oxidative stress elicited by MEHP principally injured mitochondrial function and induced the release of cytochrome c, thereby inducing apoptosis of spermatocytes and causing atrophy of the testis.

Using the 2% DEHP-dose, the effect of simultaneous administration of antioxidant vitamins (= vitamins C and E) was next examined. It was found that the vitamin supplementation significantly prevented the testicular injury. The results suggest that antioxidant vitamins can protect the testes from DEHP-toxicity.

Our recent work has elucidated that some six-carbon monosaccharides which are rarely present in nature (i.e. D-psicose and D-allose) are also effective in prevention of the testicular injury. Microarray and proteomic analyses have been applied to elucidate the genes and proteins which are involved in the DEHP-toxicity and the protection mechanism.

Effects of Estrogenic Chemicals Estimated by Gene Expression Profile

Hajime Watanabe and Taisen Iguchi

National Institutes of National Sciences, Japan

Recently, many chemicals are suspected to affect reproduction and they are called endocrine disrupters. They are considered to mimic or disturb the action of the endocrine systems. Among the endocrine disrupters, many of chemicals have been reported to have estrogenic activities. For example, nonylphenol and bisphenol A are ones of the chemicals that have been shown to have estrogenic activities. Although it is known that the chemicals can weakly bind to the estrogen receptor, it is unclear whether all reported effects of chemicals are attributable to their estrogen receptor binding activity because chemical evaluation methods had been rather limited. In order to examine if these chemicals have similar effects to the natural hormone, estradiol, we used a mouse model to examine the effects of chemicals on gene expression.

Mice (C57/BL6/J) were ovariectomized at eight weeks of age and the ovariectomized mice were injected intraperitoneally with a chemical. Total uterine and liver RNAs were extracted at 6 h after chemical administration and gene expression profiles were analyzed by mouse genome U74A (Affymetrix) Gene Chip. In addition to physiological and non-physiological estrogens, other chemicals suspected to be endocrine disrupters such as phthalates were examined. Dose dependent uterine gene expression patterns by physiological and non-physiological estrogens showed similar but distinct profiles, suggesting difference of gene activation mechanism among estrogens. In contrast to the similar effects of physiological and non-physiological estrogens observed in the uterus, in liver, gene expression was more markedly affected by non-physiological estrogens. In addition, it was found that non-physiological estrogens could activate another set of genes that is distinct from estrogen-responsive genes. These results indicate that non-physiological estrogens have similar effects to estradiol on gene expression in uterine but not in liver tissue, indicating that tissue-specific effects should be considered in order to elucidate the effects of endocrine disrupters.

Session 5 Development of Testing Methods for Endocrine Disruption

The Validation Management Group for Non-Animal Testing (VMG-NA) of the OECD Task Force for Endocrine Disrupting Testing and Assessment (EDTA)

Patric Amcoff

Organization for Economic Cooperation and Development (OECD)

At the EDTA6 meeting in Tokyo, Japan, in 2002 it was considered appropriate to establish a 3rd validation management group for development of relatively cheep and quick *in vitro* tests and screens for the level 2 of the EDTA Conceptual Framework. The group was named the "Validation Group for Non-Animal Testing (VMG-NA)" and was established in early 2003. The first meeting was held in Paris in March 2003 where a number of tests were discussed and further work outlined. At the 1st meeting it was evident that there were no tests available that had been validated and could readily be turned into official OECD Test Guidelines. However, a number of assays were considered as promising and further optimisation and pre-validation work was considered appropriate for several different tests. Four "Detailed Review Papers (DRP's)" have been developed within the areas of Steroidogenesis, Aromatase, Metabolism and Thyroid disruption (also a DRP on in vitro tests for Vitellogenin analyses has been suggested), respectively, that have provided further guidance in the selection of suitable level 2 tests. A 2nd meeting of the VMG-NA was held in October 2004 and a 3rd meeting will be held at OECD in Paris in December 2005. It is anticipated that this meeting will consider the development of a number of assays at different stages of validation, including assays for steroidogenesis, aromatase, receptor binding and transcriptional activation. Their validation status and possible inclusion in the work plan as suitable Test Guideline prospects will be discussed. Also QSAR's for ED potential are covered by the ED QSAR Task Group of the VMG-NA, which is coordinated by the VMG-NA, but monitored by the QSAR ad hoc group.

Development of OECD Test Guidelines for Endocrine Active Substances in Environmental Species

Anne Gourmelon

Organisation for Economic Cooperation and Development (OECD)

In 1997 the OECD member countries started a special activity for Endocrine Disrupters Testing and Assessment, under the umbrella of the Test Guidelines Programme. This initiative stemed from concerns that: *i)* observations from wildlife showed feminisation of fish downstream certain industries and effluent treatment plants, and *ii)* the existing OECD Test Guidelines for the testing of chemicals did not allow for the detection of substances active on the hormone systems of mammalians and wildlife species. Promising test methods were identified both for the protection of human health and the environment. Most of the methods, especially for the environment, were relatively new and brought from the science; validation was necessary to evaluate their performance and to enable regulatory acceptance.

OECD Test Guidelines are covered by the principle of the Mutual Acceptance of Data. The 1981 OECD Council Decision concerning the Mutual Acceptance of Data (MAD) in the Assessment of Chemicals is built on the OECD Test Guidelines and Good Laboratory Practice Principles (GLP). The Council Act requires OECD governments to accept chemical test data developed for regulatory purposes in another country if these data were developed in accordance with the OECD Test Guidelines and GLP Principles. This means new data for notifications or registrations of a chemical only have to be developed once, and are then used across OECD countries.

Since 2001, member countries and stakeholders from industry and environmental organisations have worked together to validate assays aimed at detecting endocrine active substances in fish, amphibians, birds and invertebrates. A Validation Management Group for ecotoxicity testing was established to oversee progress and to advise on validation issues and needs. A substantial amount of information is now available on assays using fish and amphibians, which has sometimes confirmed initial hypotheses and other times demonstrated the limits of the methods developed. Efforts to generate the data have been significant both in terms of financial resources committed and of time dedicated by all those involved: member countries and industry. With the data on the table, member countries now have to go a step further: agree on Test Guidelines and formally adopt them. This phase also requires time because OECD Test Guidelines are adopted by consensus.

A screening assay using fish has been under the validation programme to evaluate its performance: it reliably detects estrogen, aromatase inhibitors and androgens; but there are issues for the detection of anti-androgen, as demonstrated in the validation studies. The limitations of an assay are as important as its capacities in this context. The endpoints under discussion are vitellogenin, secondary sex characteristics, gonad histopathology and fecundity. An Amphibian Metamorphosis Assay is also under validation to evaluate substances active on the thyroid system; multi-chemical and multi-laboratory testing is underway. An enhanced Daphnia reproduction test, with offspring sex ratio as an indicator of endocrine activity, is considered for ring-testing. Other life-cycle or multi-generational tests including development and reproduction are evaluated and may also become part of the overall framework for testing and assessment.

The limitations of an assay are as important as its capacities in this context. To facilitate regulatory acceptance of future Test Guidelines, it will be necessary to define their scope and purpose, based on the data available. Sometimes guidance material may be added for using the data produced in the assay.

Environmental Risk Assessment of Endocrine Disrupters: Status and Needs of Biomarkers

Thomas H. Hutchinson
AstraZeneca R&D, Sweden

In order to maximise the scientific benefits of using biomarkers, they have to be biologically relevant and reproducible. This presentation will argue that biomarkers are increasingly important tools in environmental risk assessment and are best used as 'mechanistic signposts' to guide longer-term studies of adverse effects in laboratory and field populations (Hutchinson et al., 2006). Over the past decade, biomarkers have proven to be invaluable tools for tracking spatial and temporal trends in fish exposed to endocrine disrupting chemicals (EDCs). Moreover, through the use of mechanistic biomarkers such as vitellogenin induction, implications of EDC exposures for other wildlife populations (eg amphibians and birds) can be addressed in a more efficient manner. In ecotoxicology, this has the potential to provide a parallelogram approach to endocrine disrupter effects assessment, adapted from the model previously developed for mammalian genetic toxicology. For biomarkers to fulfill their potential they should be mechanistically relevant and reproducible (as measured by inter-laboratory comparisons of the same protocol). VTG is a good example of such a biomarker in that it provides an insight to the mode of action (oestrogenicity) that is vital to fish reproductive health. Inter-laboratory reproducibility data for VTG are also encouraging; recent comparisons (using the same immunoassay protocol) have provided coefficients of variation (CVs) of 38 - 55% (comparable to published CVs of 19 - 58% for fish survival and growth endpoints used in regulatory test guidelines). Biomarkers also provide linkage between field and laboratory data, playing an important role in directing the need for, and design of, fish chronic tests for EDCs. It is the adverse effect endpoints (e.g. altered development, growth and/or reproduction) from such tests that are most valuable for calculating ^{adverse}NOEC (No-Observed Effect Concentration) or ^{adverse}EC10 (concentration giving a 10% effect) and subsequently deriving Predicted No-Effect Concentrations (PNECs). With current uncertainties, ^{biomarker}NOEC or ^{biomarker}EC10 data should not be used in isolation to derive PNECs. In the future, however, there may be scope to increasingly use biomarker data in environmental decision-making, if plausible linkages can be made across levels of organization such that adverse outcomes might be envisaged relative to biomarker responses.

Background references: Handy et al (2003) Ecotoxicology 12: 331-343; Hutchinson et al., (2006) Environ. Hlth. Perspect (special issue); Sumpter & Jobling (1995) Environ. Hlth. Perspect., 103 (suppl 7):173-178; van der Oost et al (2003) Environ. Toxicol. Pharmacol., 13: 57-149.

Session 6 Current Initiatives on Risk Assessment of Chemicals

Roadmap for Implementing the USEPA Endocrine Disrupter Screening Program

Karen Whitby

U.S. Environmental Protection Agency (EPA), U.S.A

Under the Food Quality Protection Act (FQPA) of 1996, the United States Environmental Protection Agency (US EPA) is required to develop a chemical screening program for pesticides and environmental contaminants to determine if these substances may have an effect in humans and wildlife that is similar to an effect produced by a naturally occurring estrogen, or such other endocrine effect as the Administrator may designate. With the input of a federal advisory process, the Agency developed a two-tiered approach for an Endocrine Disrupter Screening Program (EDSP) to carry out Congress' directives. There are over 1,000 pesticide active ingredients, and over 2,700 pesticide inert ingredients that are eligible for screening under FQPA. One of the greatest challenges the Agency faces is the development of tools to identify available, relevant information to prioritize data needs for testing and risk assessments. EPA is implementing the EDSP in three major steps: 1) Develop and validate the screening level Tier 1 assays and Tier 2 tests. (Tier 1 assays are intended to identify the potential of chemicals to interact with hormone systems, while Tier 2 tests are designed to determine if the pesticide chemical causes endocrine effects that may be quantitated in a dose-response relationship.) 2) Develop the procedures the Agency will use to require screening. 3) Finalize the priority setting for selecting the initial list of chemicals to undergo screening. The Office of Research and Development within the US EPA is conducting ongoing research and development for *in vitro* and *in silico* techniques to aid in pre-screening chemicals. This research is being conducted in concert with the OECD QSAR Task Group.

This abstract has been subjected to review by EPA's Office of Pesticide Programs and was approved for submission. Approval does not signify the contents reflect the views of EPA, nor does mention of trade names or commercial products constitute endorsement or recommendation for use.

Developing Approaches to Chemicals Management - A UK View

Michael John Roberts

Department for Environment, Food and Rural Affairs (Defra), U.K.

The development of national and international policies on the management of chemicals continues to be a dynamic area, with several initiatives in progress.

Within the European Union, work is underway to establish a more effective system to assess the short and long-term risks posed by industrial chemicals and to take action where necessary - referred to as the Registration, Evaluation and Authorisation of Chemicals (REACH).

In addition, the EU has launched an "Environment & Health Strategy", known as SCALE (Science, Children, Awareness, Legal Instruments, Evaluation), which aims to establish a good understanding of the link between environmental factors (including chemicals) and:

* Childhood respiratory diseases, asthma and allergies;
* Neurodevelopmental disorders;
* Childhood cancer;
* Endocrine disrupting effects.

Similarly, regional priority goal 4 of the World Health Organisation (Europe) led initiative on Environment & health - the Children's Environment & Health Action Plan for Europe (CEHAPE) - requires action on hazardous chemicals.

There are also currently a number of international agreements on chemicals management - for example: *the Stockholm Convention on Persistent Organic Pollutants (POPs) and the Rotterdam Convention on the Prior Informed Consent Procedure for Certain Hazardous Chemicals and Pesticides in International Trade.*

At the same time as working with European partners to develop more effective EU legislation, the UK Government is working with stakeholders to develop solutions that can be applied to reduce the risk of chemicals damaging the environment, at national level.

Japan's Approach for the Prevention of Environmental Pollution Caused by Chemicals

Satoru Morishita

Ministry of the Environment, Japan

Law concerning the Evaluation and Regulation of Industrial Chemicals

Due to increasing concerns about environmental pollution caused by industrial chemicals such as PCBs, the Law concerning the Evaluation of Chemical Substances and Regulation of their Manufacture, etc. was enacted in Japan in October 1973. The aim of the Law was to prevent environmental pollution by chemicals that had PBT properties (i.e. persistency, bioaccumulation and toxicity) in order to protect human health. Since then, the manufacture and import of the designated PBT chemicals as "Class I Specified Chemicals" have strictly been prohibited. This regulation has contributed a lot to avoid environmental pollution of POPs.

In 1991, the Law was amended aiming to improve international harmonization of chemical regulation as well as to address the pollution caused by non-PBT chemicals, such as trichloroethylene and tetrachloroethylene. These chemicals are not highly bioaccumulative, however their persistency and toxicity have still potential for posing environmental problems. At that time, the control of these chemicals was ensured by introducing a risk-based approach into the Law, and based on the results of the assessments it was legally enabled to put upper limits on the annual production/import volume for designated chemicals as "Class II Specified Chemicals".

More recently, in 2003, the Law was further amended by incorporating the protection of the ecosystem to its purpose, which came into effect in April 2004. At that time, the regulations of the Law were also streamlined for improving its efficiency by putting more attentions to the likelihood of emissions of chemicals to the environment.

Environmental Monitoring and PRTR

The environmental survey and monitoring have systematically been carried out in Japan, and their outcome has been used as major input to environmental exposure assessments of chemicals.

Japan's Ministry of the Environment (JMoE) has initiated an environmental monitoring program in 1973 in cooperation with local governments. This program covers multi-environmental media (i.e. water, sediment, biota and air) of all over Japan, and has successfully provided useful data. In some cases, they got triggers of taking action under the above Law.

Utilizing its experience, JMoE advocated a creation of the POPs environmental monitoring program at the East Aisin region in 2002. After that, with strong supports from the countries in the region, JMoE have held a series of workshops on environmental monitoring of POPs.

Japan's PRTR has started in 1999. The PRTR data have been used in carrying out exposure assessment of chemicals.

Environmental Basic Plan

In Japan, the work for developing the 3rd Environmental Basic Plan has been progressing. The Environmental Basic Plan is a governmental one where comprehensive measures for protecting the environment are set out. The 3rd the Plan will set targets for the next two decades. It will be released around the end of 2005, and a strategic plan for the reduction of risks caused by chemicals will be a part of the Plan in order to tackle outstanding issues that still remain in that area, such as acceleration of examination of industrial existing chemicals.

化学物質の内分泌かく乱作用（いわゆる環境ホルモン作用）について、環境省は1998年から取組を進めてきました。この間に化学物質の内分泌かく乱作用に関する様々な知見が集積したことを受け、2005年3月環境省は、現時点まで取組の成果をとりまとめ、また、今後の取組指針を示すものとして「化学物質の内分泌かく乱作用に関する環境省の今後の対応方針について-ExTEND2005（エクステンド2005）-」を公表しました。

2005年4月からは、このExTEND2005に沿って、総合的な化学物質対策の中で、野生生物の観察、環境実態調査、基盤的研究、試験法開発、リスクコミュニケーションの推進といった、より一層幅広い取組を進めています。

この国際シンポジウムは、環境省が内分泌かく乱作用に関する取組の一環として、1998年から毎年実施しているもので、今年度で第8回目を迎えます。今回から、ExTEND2005のタイトルにあわせ、名称を「化学物質の内分泌かく乱作用に関する国際シンポジウム」へと改めました。
また、ExTEND2005において、情報提供・リスクコミュニケーションの推進や国際協調の重要性が強調されていることを受け、シンポジウムの位置づけを、一般向けプログラムについては「一般市民の皆様との情報共有の場」、専門家向けプログラムについては「国内外の専門家の方々の意見交換の場」と明確に示し、シンポジウムがより一層有意義なものとなるよう努めています。

この国際シンポジウムが、化学物質の内分泌かく乱作用について、さらに化学物質対策についての情報共有の場として、また専門的な意見交換の場として、広く活用されることを願っています。

2005年11月

事務局一同

Participants of the International Symposium on Endocrine Disruption:

The Ministry of the Environment of Japan (MOE) had conducted various measures on the endocrine disrupting effects of substances since 1998. Based on the scientific knowledge accumulated thorough these activities, in March 2005 MOE released "MOE's Perspectives on Endocrine Disrupting Effects of Substances - ExTEND2005 -" as a summary of its activities to date and also as a new guideline for subsequent initiatives on the issue.

Since April 2005, in accordance with ExTEND2005, MOE has been promoting activities with a broader scope as part of a comprehensive approach to chemical issues. The main areas covered are: observation of wildlife, environmental monitoring, fundamental research, technological development and risk communication.

MOE has been holding this annual international symposium since 1998 to facilitate international cooperation on the issue of endocrine disruption, and this is the 8th symposium. From this year, the title has changed to "International Symposium on Endocrine Disruption" for consistency with the basic principals of ExTEND2005. As ExTEND2005 establishes the need to promote information sharing, risk communication and international cooperation, MOE has set two clear aims for the symposium: information sharing with the general public in respect of the program for general audiences and exchange of knowledge and opinions among foreign and domestic experts in respect of the program for experts.

We hope this year's symposium will be a significant opportunity for all participants to share information and exchange wide-ranging opinions on the issue of endocrine disruption in the context of comprehensive strategies for chemicals.

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The Secretariat

環境省総合環境政策局環境保健部環境安全課

〒100-8975　東京都千代田区霞が関 1 丁目 2 番 2 号
TEL: 03-3581-3351（内線6354）FAX: 03-3580-3596　E-mail: eri_muto@env.go.jp

Environmental Health and Safety Division
Environmental Health Department
Ministry of the Environment, Government of Japan

1-2-2 Kasumigaseki, Chiyoda-ku, Tokyo 100-8975, Japan
TEL: +81-(0)3-3581-3351 (Ext :6354) FAX: +81-(0)3-3580-3596 E-mail: eri_muto@env.go.jp

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